REMARKS

The above amendments to the above-captioned application along with the following remarks are being submitted as a full and complete response to the Office Action dated May 25, 2006 (U.S. Patent Office Paper No. 03282006). In view of the above amendments and the following remarks, the Examiner is respectfully requested to give due reconsideration to this application, to indicate the allowability of the claims, and to pass this case to issue.

Status of the Claims

As outlined above, claims 1-4 stand for consideration in this application, wherein claims 1-3 are being amended to correct formal errors and to more particularly point out and distinctly claim the subject invention. In addition, new claim 4 is hereby submitted for consideration. The claims as amended herein are fully supported by the application as originally filed. No new matter has been added.

Formal Objections or Rejections

Claims 1-3 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Prior Art Rejections

Claims 1-2 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Chrisey et al. (U.S. Patent No. 5,688,642).

Claims 1 and 3 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Chrisey et al. (U.S. Patent No. 5,688,642) in view of Okinaka et al. (U.S. Patent No. 5,155,190).

Claims 1 - 3 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Koster et al. (U.S. Patent No. 6,133,436) in view of Siimian et al. (U.S. Patent No. 5,945,293).

Claim Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-3 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner asserts that although the claims recite a "method of manufacturing a nucleic acid array", that the steps do not in fact result in an

"array." Further, the Examiner questioned the lack of antecedent basis for "the second region."

Applicants have amended the claims to more distinctly and precisely claim the subject matter of the invention and said amendments have obviated this ground for rejection and it is respectfully asked that it be withdrawn.

Claim Rejections under 35 U.S.C. § 102(b)

Claims 1-2 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Chrisey et al. (U.S. Patent No. 5,688,642). The Examiner, by citing portions of the Chrisey et al. patent, allege that Chrisey et al. has taught what is claimed in claims 1-2. Applicants disagree and hereby traverse as follows.

Applicants' assignment of error is failure to appreciate the patentably unique method of derivatizing the functional groups of the second region, without the need for extrinsic blocking agents in order to provide a unique electrostatic effect advantageous to nucleic acid detection using the immobilized hybridizable probes of the present invention. As amended, the claims are directed to a method for attaching an array of single-stranded hybridizeable nucleic acid probes for use in detecting nucleic acids by hybridization comprising the steps of: providing a substrate having a surface on which maleimide functional groups are formed; covalently immobilizing said probes unto said surface using said functional groups to form a first region comprising the covalently immobilized probes and a second region wherein the probes are not covalently immobilized; hydrolyzing unreacted maleimide functional groups on the second region to form new functional groups which are negatively charged in an aqueous environment.

The maleimide group can be hydrolyzed to negatively charged maleamic acid. Because functional groups that become negatively charged by dissociation in an aqueous solution are present on the surface of the second region where no probe is immobilized, the electrostatic repulsion between a negatively charged nucleic acid target and the negatively charged functional groups in the second region prevent nonspecific adsorption of the nucleic acid target. (see summary of the invention, page 4 lines 22 of the specification; paragraph [0006] of the corresponding JP publication).

In addition, the maleamic acid groups have a higher blocking effect due to the electrostatic repulsion between the negative charge of the nucleic acid and the negative charge of the maleamic acid than the blocking agents disclosed in the alleged prior arts. As a

result, a high hybridization signal is obtained while a background signal is substantially suppressed (See Figs. 2 and 3). These results are not achievable with the alleged prior art.

Applicants will now proffer further reasons why the blocking action of maleic acid is further accentuated by electrostatic repulsion with target nucleic acids in ways that are patentably unobvious, let alone anticipated by any other prior art including Chrisey et al.

Virtually every blocking agent of note is immobilized on a maleimide substrate by physical adsorption. Adsorption, by definition, involves relatively weak binding forces leading to substantial risk that blocking agents physically adsorbed to the maleimide substrate could become dislodged during the hybridization process.

Furthermore, many of the blocking agents known in the art have high molecular weights. As a result, their rate of blocking of the maleimide group on the substrate is low. Further, the percentage of negatively charged functional groups per unit area is also low.

Further, although it is possible that a blocking agent having an amino group covalently bonds with a maleimide group, the rate of coupling reaction between an amino group and a maleimide group is smaller than that between a sulfhydryl group (claim 2, a thiol group) and a maleimide group, resulting in a high possibility that unreacted maleimide groups remain on the substrate.

Also, the rate of hydrolysis of maleimide depends greatly on the pH, so that a higher rate of hydrolysis can be achieved by performing hydrolysis using a solution with higher pH (claim 3, alkaline solution). The advantage is that the amount of unreacted maleimide groups remaining on the substrate is small.

Additionally, in accordance with the invention, a maleamic acid having a high blocking effect can be introduced onto the substrate simultaneously with the process of eliminating unreacted nucleic probes. In the prior art examples, a new blocking step is required after removing the unreacted nucleic acid probes. Thus, the number of steps and the manufacturing cost are lower in accordance with the invention.

With the many unobvious advantages of the present invention made clear. Applicants will now specifically refute the citations in Chrisey et al. erroneously deemed to teach explicitly or inherently what is claimed in the present invention.

Regarding Col.3, lines 39-57; col. 7, line 65 to col. 8, line 13; Figs. 1 and 3; col. 6, lines 33-44; Chrisey et al. in no way taught or suggested the hydrolysis of unreacted maleimide groups to malemic acid in order to provide both an electrostatic repulsion and to accentuate the blocking effect.

Regarding Col. 7, lines 15-20; Chrisey et al. discloses blocking effect due to a blocking agent. However, the blocking action of the malemic acid of the present invention provides patentably substantial advantages over any blocking mechanism taught or suggested by Chrisey et al. Most advantageously, the high blocking effect of the present invention can be introduced onto the substrate simultaneously with the process of eliminating unreacted probes unlike Chrisey et al. that requires a new blocking step after removing the unreacted nucleic acid probes.

As to Chrisey's teaching of protein and carbohydrates as blocking agents, these high molecular weight blocking agents are hampered by low blocking rates. Regarding Chrisey's teaching of detergents as blocking agents, the use of weak physical adsorption forces makes the blocking agent susceptible to dislodgment. As to Chrisey's teaching of amino acids as blocking agents, the rate of coupling reaction between an amino group and a maleimide group is smaller than that between a sulfhydryl group (claim 2, a thiol group) and a maleimide group, resulting in low blocking ratio.

Regarding Example 9, Fig. 3, cited by the Examiner as anticipatory to claim 2 of the present invention, Applicants point out that washing with a buffer of pH 7.6 for eliminating unreacted non-covalently bound DNA is described. However, nothing is stated about the region where no probe is bonded. In accordance with the present invention, the region where no probe is bonded is actively hydrolyzed, whereby a high blocking effect due to the electrostatic repulsion between the negative charge of a maleamic acid, which is a hydrolysis product, and the negative charge of a nucleic acid is obtained.

As the Examiner is aware, a claim is anticipated under 35 U.S.C. §102(b) only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *See Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claim. *See Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989). Moreover, elements must be arranged as required by the claim. *See In re Bond*, 910 F.2d 831(Fed. Cir. 1990). Not only does Chrisey et al. not teach what is claimed in the instant invention, it does not even suggest the blocking methodology of the instant invention. As such, for at least the foregoing, Applicants assert that there is no basis for rejection under 35 U.S.C. § 102 and respectfully ask that this ground for rejection be withdrawn.

Claim Rejections under 35 U.S.C. § 103(a)

Claims 1 and 3 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Chrisey et al. (U.S. Patent No. 5,688,642) in view of Okinaka et al. (U.S. Patent No. 5,155,190).

Further, claims 1 - 3 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Koster et al. (U.S. Patent No. 6,133,436) in view of Siimian et al. (U.S. Patent No. 5,945,293).

The Examiner basically asserts that Chrisey et al. teaches identically what is claimed but is otherwise silent with respect to alkaline solution and that that deficiency is cured by Okinaka et al.which teaches hydrolysis of maleimide at alkaline pH. (Col. 6, lines 16 – 20). Applicants disagree and respectfully traverse as follows.

The cited portion of Okinaka et al. (Col. 6, lines 16-20) allegedly curative of the deficiency of Chrisey et al. merely describes the hydrolysis of a maleimide group. There is no description regarding the blocking effect due to the electrostatic repulsion between the negative charge of a maleamic acid as a hydrolysis product and the negative charge of a nucleic acid, according to the present invention. Thus, not only would the present invention not be attained by a combination of Chrisey et al and Okinaka et al, both references are not combinable.

In order to combine prior arts, both the suggestion to do so and the expectation of success must be founded in the prior art, not in the applicant's disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir, 1988). As a matter of law, therefore, the mere fact that the prior art could be so modified would not make the modification obvious unless the prior art suggested the desirability of the modification. In re Laskowski, 871 F.2d 115, 10 USPQ2d 1397 (Fed. Cir. 1989). The Examiner points out that the asserted rapid hydrolysis of maleimide taught by Okinaka et al. is a motivation to make the combination. The controlling issue is not that rapid hydrolysis may be attained but why one should do so in the first place. Because neither Okinaka nor Chrisey motivates or suggests the desirability of doing the hydrolysis to attain the effects of the present invention, the combination is definitely not proper. There being no basis for this ground for rejection, Applicants respectfully ask that it be withdrawn.

Regarding claims 1 - 3 rejected under 35 U.S.C. § 103(a) as allegedly obvious over Koster et al. (U.S. Patent No. 6,133,436) in view of Siimian et al. (U.S. Patent No. 5,945,293), Applicants reiterate the foregoing arguments.

More particularly, Koster et al. Col. 5, lines 5-20, only describes an immobilizing method using a maleimide group. No description of the blocking effect due to a hydrolysis product of a maleimide group according to the present invention was suggested or taught.

Similarly, Siimian et al. Col. 22, lines 59-65, only describes an immobilizing method using a maleimide group. No description of the blocking effect due to a hydrolysis product of a maleimide group according to the present invention was suggested or taught. Most particularly, Col. 23, lines 49-53, col. 10, lines 61-63 of Siimian et al. describes a blocking agent being the amino acid L-cystein. The disadvantages of using amino acids has been mentioned above, not to mention the advantage of generating the blocking effect simultaneous with removing unreacted probes. Further, Siimian et al. Col. 16, lines 23-27 describes washing with a buffer of pH 7.2 for eliminating unreacted non-covalently bound DNA. However, nothing is stated about the region where no probe is bonded. In accordance with the present invention, the region where no probe is bonded is actively hydrolyzed, whereby the blocking effect due to the electrostatic repulsion between the negative charge of a maleamic acid, which is a hydrolysis product, and the negative charge of a nucleic acid is obtained.

Not only would the combination of Koster and Siimian not teach the present invention, the Examiner has not pointed to any teaching or suggestion in the asserted art to make the combination which the Examiner deems obvious. Specifically, Col. 10, lines 61 – 63, deemed by the Examiner to provide the motivation for the combination states: "Preferably before use, unreacted functional groups on the resulting stable colloidal particles are blocked with appropriate blocking agents, such as L-cysteine and iodoacetamide." In point of fact, therefore, the only motivation the Examiner can point to is the "use of appropriate blocking agents," which is a total departure from the methodology of the present invention which generates blocking effect without using the so called "appropriate blocking agents."

Applicants respectfully ask that this ground for rejection be also withdrawn.

Conclusion

In view of the foregoing, Applicants believe that all the grounds for rejection have been rendered moot or otherwise traversed. The claims as amended are in position for allowance and Applicants earnestly solicit early notification of allowability from the

Examiner. Should the Examiner have any questions or believe a personal or telephone interview may be in order, he is invited to contact the undersigned at his earliest convenience.

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